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[A0035]

Synthesis of Rigid Acetylcholine Mimics as Inhibitors of Serine Hydrolases

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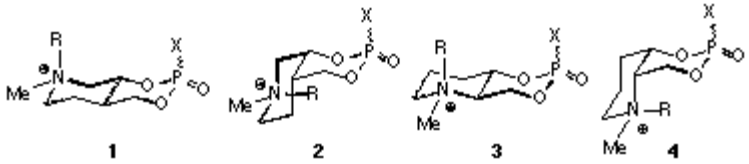
Abstract: In continuation of our investigations concerning the regio- and stereo-chemical course of the inhibition of serine hydrolases (chymotrypsin, acetylcholinesterase) (F.A. Merckling, P. Rüedi, *Chimia* **1994**, *48*, 279) we have prepared conformationally restricted organophosphates of the *cis*- and *trans*-az(oni)adecaline type. Related compounds proved to be good probes for the investigation of stereochemical implications by ^{31}P-NMR spectroscopy (W. Ganci, E.J.M. Meier, F.A. Merckling, G. Przibille, U. Ringeisen, P. Rüedi, *Chimia* **1996**, *50*, 345; iid. *Helv. Chim. Acta*, **1997**, *80*, 421).

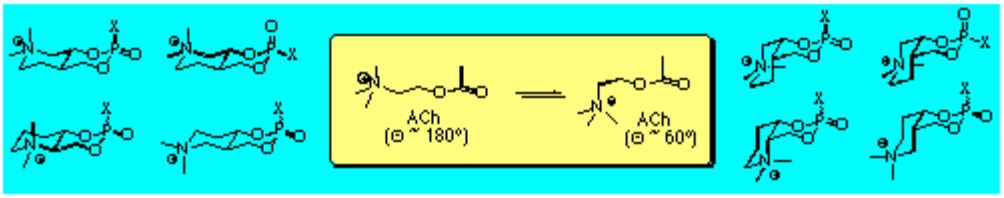


X = good leaving group, axial and equatorial epimers
R = :, H, Me, CH_2Ph

The inhibitors, representing different conformations of a phosphorous analogue of acetylcholine were prepared from the corresponding N-protected oxopiperidine carboxylic acid esters. Kinetic characterization showed the *cis*-fused heterocycles **2** and **4** to be reversible inhibitors of acetylcholinesterase (K_i~10^{-7} M), whereas the*trans*-isomers of type **1** inhibit the enzyme irreversibly (k_i~10^4 $M^{-1}sec^{-1}$).

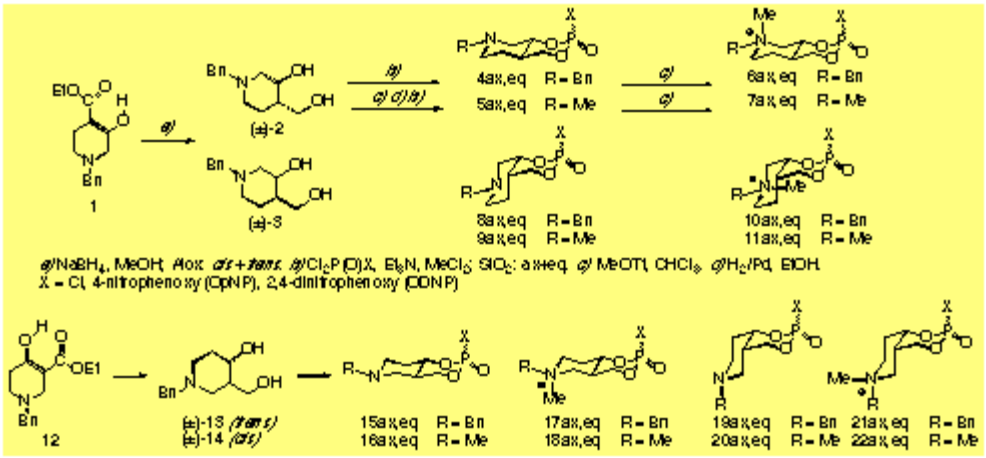
Introduction

In our studies concerning the regio- and stereochemical course of the inhibition of serine hydrolases we use 2,4-dioxa-3l^5-phosphabicyclo[4.4.0]decan-3-ones. Being configurationally and conformationally locked, these decaline-type congeners are good probes for the investigation of reaction pathways by ^{31}P-NMR spectroscopy [1]. In the course of a recent project we have prepared novel *cis*- and *trans*-N-heterocyclic organophosphates as rigid mimetics of acetylcholine (ACh) [2]. The compounds represent different conformations of ACh (g-*homo*-ACh, resp.) and are supposed to enable the investigation of conformational implications in the inhibition reaction.



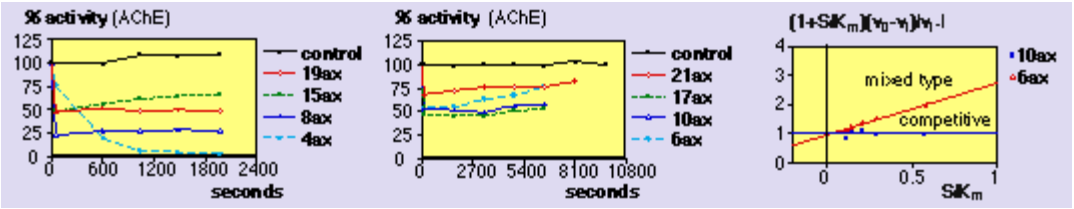
Synthesis

The bicyclic organophosphates were synthesized from the esters **1** (**4**-**11,** ACh-types) and **12** (**15**-**22**, g-*homo*-ACh types) *via* the corresponding *rac.* diols as exemplified in the scheme. Attempts to prepare the isomeric ACh-type from ethyl (1-benzyl-3-oxopiperidin-2-yl)carboxylate (the kinetic product of the *Dieckmann* condensation of ethyl 4-[*N*-benzyl-*N*-(ethoxycarbonylmethyl)amino]butanoate) resulted in hitherto unseparable mixtures of the dihydroxypiperidines or derivatives thereof. The compounds have been fully characterized; due to stereoelectronic reasons, only the axial epimers could be isolated when X=Cl or X=ODNP.



Inhibitory Activity

Kinetic investigations (see graphs) revealed only the 'ACh-like' *trans*-congeners **4ax** to be weak irreversible inhibitors of a-chymotrypsin (BTEE-assay, pH 7.8, computation according to [3]) and AChE (PNPA-assay, pH 7.0, according to [4]). The following k_i-values [$M^{-1}sec^{-1}$] have been determined: 0.75 (X=Cl), 58.5 (X=ODNP) for a-chymotrypsin and $2 \cdot 10^4$ (X=Cl), $1.02 \cdot 10^3$ (X=OPDNP) for AChE. The other compounds turned out to be reversible inhibitors of AChE: **8ax**, **10ax**, **15ax**, **19ax**, and **21ax** were shown to be competitive ($K_i \sim 10^{-6}$-10^{-7}M), whereas **6ax** and **17ax** belong to the linear mixed type ($K_i \sim 10^{-6}$). The differentiation between the various types of reversible inhibition was performed according to [5] as depicted in graph 3 for a representative sample pair. The dimethylammonium derivatives are currently being investigated.



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[1] F.A. Merckling, P. Rüedi, *Chimia* **1994**, *48*, 279; W. Ganci, E.J.M. Meier, F.A. Merckling, G. Przibille, U. Ringeisen, P. Rüedi, *Helv. Chim. Acta*, **1997**, *80*, 421; S. Furegati, Diploma Thesis, University of Zurich 1997.

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Comments

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